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Iron deficiency in pulmonary hypertension: from observation to intervention

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Summary

Part I

The first part of this thesis described the prevalence, causes, consequences and treatment strategies of iron deficiency (ID) in pulmonary hypertension (PH).

First, the prevalence of ID in patients with idiopathic pulmonary arterial hypertension (IPAH) was investigated in **Chapter 2**. We found that ID was very common in IPAH patients with a point prevalence of 43%. Interestingly, ID patients had a lower mean 6-min walking distance (6MWD) than non-iron deficient (non-ID) patients, although haemodynamics were similar between the two groups. Oral iron treatment in a subset of patients revealed that almost half of the patients did not increase body iron stores and remained iron deficient after treatment.

A similar study was performed in another group of patients in **Chapter 3**. Iron parameters were measured in patients with systemic sclerosis with (SSc-PH) and without PH (SSc-nonPH). SSc-PH patients were more often iron deficient than SSc-nonPH patients. In addition, exercise capacity by means of 6MWD and cardiopulmonary exercise testing, was lower in ID than in non-ID patients in both the SSc-PH and SSc-nonPH group. Furthermore, four-year survival was significantly poorer in ID SSc-PH patients compared with non-ID SSc-PH patients, and a similar trend was observed in SSc-nonPH patients.

In **Chapter 4**, oxygen supply parameters were studied in more detail in hearts of patients who died from right heart failure due to PH or who died after a left ventricular myocardial infarction (MI) without PH. Right ventricular cardiomyocyte cross-sectional area of PH patients was significantly larger than of MI patients, with decreased capillary density. In addition, myoglobin concentration was lower in PH than in MI patients. These results were confirmed in a PH rat model and it was shown that the underlying cause of the low right ventricular myoglobin resulted from a lack of increase in myoglobin mRNA transcription per cardiomyocyte nucleus. This study demonstrated that, although myocardial oxygen consumption is increased in the right ventricle in PH, all cellular oxygen supply parameters are decreased.

The first chapters showed that ID is common in PH patients and associated with worse exercise capacity and survival, and could not be reversed with oral iron treatment. Therefore, in **Chapter 5**, we treated IPAH patients with a high dose of intravenous iron (Ferric carboxymaltose, Ferinject®). Twelve weeks after intravenous iron treatment, body iron stores were increased in all patients. Submaximal exercise endurance time was significantly improved and the anaerobic threshold was delayed. Cardiac function was unchanged, but quality of life was significantly better after iron treatment. Histology analysis of quadriceps muscle biopsies from the patients revealed higher myoglobin levels and mitochondrial oxidative capacity in low oxidative fibers after iron therapy, without alterations in capillarisation.

In the same chapter, the development of PH under ID circumstances was studied in an ID PH rat model. PH development was similar in PH rats with and without ID, but there were several differences at the cellular level in the right ventricle. ID PH rats showed higher right ventricular capillarisation with lower myoglobin concentrations and mitochondrial oxidative capacity than non-ID PH rats, which could be restored by iron supplementation. Interestingly, iron supplementation decreased the pulmonary artery muscularisation. In the skeletal muscles, similar observations as in the human study were found: myoglobin and mitochondrial oxidative capacity were reduced in ID PH rats compared with non-ID PH rats and could be increased by iron supplementation.

Part II

The second part of this thesis described several approaches to study PH in humans and rats.

First, an animal model of PH was studied in **Chapter 6**. The natural course of a low-dose monocrotaline PH rat model (i.e. 40 mg/kg) was investigated. It was demonstrated that PH was present 4 weeks after monocrotaline injection, which was characterised by echocardiography, right heart catheterisation and histological analysis. However, after 8 and 12 weeks of monocrotaline injection, no signs of PH were present. This type of model is therefore not suitable for therapeutic studies longer than 4 weeks after a low dose of monocrotaline.

Although the right ventricle has been studied intensively, the role of the interventricular septum (IVS) in PH is still poorly understood. Therefore, we initiated a study to investigate several characteristics of the total IVS in IPAH patients, and at a cellular level in a PH rat model. **Chapter 7** shows that total IVS mass and glucose uptake was associated with the left ventricular free wall but not with the right ventricular free wall. In addition, at the cellular level, the right side of the IVS showed hypertrophy but signs of right heart failure, such as fibrosis and inflammation, were absent in the IVS.

In **Chapter 8**, a non-invasive method to measure pulmonary uptake of a radioactively labelled glucose-analogue 2-deoxy-2-[¹⁸F]-fluoro-D-Glucose (FDG) was tested with positron emission tomography in IPAH patients and compared with patients who had an LV MI. Total standard uptake values of FDG were similar in IPAH and MI patients and there was no correlation between FDG uptake and IPAH disease severity parameters. Furthermore, pulmonary FDG uptake did not predict survival in IPAH patients, limiting the use of this method in clinical PH care.

All results from this thesis and directions for future research are discussed in **Chapter 9**.